First-in-human study of tisotumab vedotin in advanced and/or metastatic solid tumours: a multicentre, phase 1/2 trial

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ABSTRACT

Background. Tisotumab vedotin (TV; HuMax-TF-ADC), is a first-in-class antibody-drug conjugate directed against tissue factor (TF), which is expressed across multiple solid tumor types and is associated with poor clinical outcomes. The primary objective of this study was to establish the tolerability of TV in a mixed population of patients with specified solid tumors.

Methods. InnovaTV 201 is a phase 1/2 open-label, dose-escalation and -expansion study evaluating the safety, tolerability, pharmacokinetics (PK) profile, and antitumor activity of TV in patients with locally advanced and/or metastatic solid tumors known to express TF. Patients were aged ≥18 years and had an ECOG PS of 0-1. No specific TF expression level was required for inclusion. In the dose-escalation phase, patients were treated with TV between 0·3 and 2·2 mg/kg intravenously once every 3 weeks in a traditional 3 + 3 design to determine the maximum-tolerated dose (MTD) and recommended phase 2 dose (RP2D). Plasma was collected to characterize the PK profile of TV. In the dose-expansion phase, patients were treated at the RP2D in seven advanced solid tumor-type cohorts, including bladder, cervix, endometrium, esophagus, lung, ovarian, and prostate cancers. The primary endpoint of the study was the incidence of adverse events, which was analyzed in all patients who received at least one dose of TV. This study is registered with ClinicalTrials.gov, number NCT02001623, and is closed to new participants with follow-up ongoing.

Findings. In the dose-escalation phase, 27 patients with advanced solid tumors received TV in eight sequential dose cohorts between 0·3 and 2·2 mg/kg. Dose-limiting toxicities, including grade 3 type 2 diabetes mellitus, mucositis, and neutropenic fever, were observed at TV 2·2 mg/kg. TV at 2·0 mg/kg was identified as the MTD and the RP2D. The PK profile of TV was dose proportional. In the dose-expansion phase, 147 patients with solid tumors were treated with

TV at 2·0 mg/kg. The most common (≥20%) treatment-emergent adverse events (AEs) of any grade included epistaxis (102 [69·4%] of 147 patients), fatigue (82 [55·8%]), nausea (77 [52·4%]), alopecia (64 [43·5%]), conjunctivitis (63 [42·9%]), decreased appetite (53 [36·1%]), constipation (n=52 [35·4%]), diarrhea (44 [29·9%]), vomiting (42 [28·6%]), neuropathy peripheral (33 [22·4%]), dry eye (32 [21·8%]), and abdominal pain (30 [20·4%]). The most common AEs of ≥3 grade included fatigue (14 [9·5%] of patients), anemia (8 [5·4%]), abdominal pain (6 [4·1%]), hypokalemia (6 [4·1%]), conjunctivitis (5 [3·4%]), hyponatremia (5 [3·4%]), and vomiting (5 [3·4%]). Treatment-emergent serious AEs (SAE) occurred in 67 (45·6%) of 147 patients; a total of 39 (26·5%) of 147 patients experienced a treatment-emergent SAE related to the study drug. Across tumor types, the confirmed ORR was 15·6% (95% CI: 10·2%–22·5%; 23 of 147 patients).

Interpretations. TV demonstrated a manageable safety profile with encouraging preliminary antitumor activity across multiple tumor types in heavily pretreated patients. Based on these data, continued evaluation of TV is warranted in solid tumors.

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RESEARCH IN CONTEXT

Evidence before the study

We performed a search through August 19, 2018 to identify all clinical studies evaluating the use of tissue factor (TF)-targeting therapeutics in patients with cancer. Our search included PubMed and used the following search terms: “tissue factor,” or “thromboplastin,” or “CD142.” TF is broadly expressed across multiple solid tumor types and contributes to cancer biology by promoting metastasis, tumor growth and tumor angiogenesis, suggesting that it may be a potential target for therapeutic intervention. Our search revealed that no studies have been published on the safety and activity of TF-targeting agents in patients with cancer; although two early phase clinical trials evaluated agents in patients with macular degeneration or acute lung injury.

Added value of this study

To our knowledge, this is the first study assessing the safety, tolerability, pharmacokinetics, and preliminary activity of a TF-targeting agent, tisotumab vedotin (TV), in patients with cancer. In this phase 1/2 study, TV demonstrates a manageable safety profile and preliminary activity in patients with advanced solid tumors, including bladder, cervix, endometrium, esophagus, lung, and ovary.

Implications of all the available evidence

The prognosis for patients with advanced solid tumors remains poor and there is an unmet need for new treatments to improve outcomes. The present trial confirms the feasibility and preliminary clinical activity of tisotumab vedotin, a TF-targeting antibody drug conjugate, in patients with locally advanced and/or metastatic solid tumors known to express TF. Further

studies are required to confirm this activity and assess in which patients TV is most likely to be effective.

INTRODUCTION

Tisotumab vedotin (TV) is a first-in-class antibody-drug conjugate (ADC) that is directed against tissue factor (TF) expressed on the cell surface of tumor cells to deliver a clinically validated toxic payload to tumors.[1,2] TV is comprised of a fully human monoclonal antibody specific for TF conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable valine-citrulline linker.[1]

TF is a transmembrane glycoprotein that functions as the main initiator of the TF pathway of blood coagulation, also known as the extrinsic coagulation pathway.[3,4] Beyond its function in coagulation, TF has cell-signaling properties.[5] TF, in complex with its physiological ligand FVIIa, can activate protease-activated receptor 2, resulting in an intracellular-signaling cascade that tumors can exploit to promote malignant-cell survival, tumor growth, angiogenesis, and metastasis.[3,5,6] The role of TF in cancer biology is underscored by its aberrant expression in a broad range of solid tumors. For example, high percentages of TF-positive tumor biopsies, as assessed by immunohistochemistry, were observed in cervical cancer (100%), non-small cell lung cancer (34–88%), endometrial cancer (14–100%), prostate (47–75%), ovarian cancer (75–100%), esophageal cancer (43–91%), and bladder cancer (78%).[7–18] The expression of TF is enhanced in cancer through oncogenic events, such as constitutive activation of the MAPK- and PI3K-signaling pathways, hypoxia-induced signaling, and loss of tumor suppressor genes.[3] TF expression levels have been associated with poor clinical outcomes and higher metastatic potential in multiple solid tumor types.[6,18,19] Treatment options for many of these solid tumors remain limited and, especially in the context of metastatic and refractory disease, are often hampered by poor efficacy and/or significant toxicities. There is an urgent unmet medical need for more effective and tolerable treatment alternatives for patients with these types of cancer.

Given its differential expression in many cancers as well as its role in cancer biology, TF is a rational target for the development of therapeutics to help address this unmet need and the potential to improve patient outcomes across a broad range of solid tumors.

The antibody moiety of TV, HuMax-TF, was selected from a panel of TF-specific human monoclonal antibodies based on high affinity binding to TF (low nM range) and the capacity for interfering with protease activated receptor 2 (PAR-2) intracellular signaling, as assessed by inhibition of TF:FVIIa-dependent ERK phosphorylation and interleukin (IL)-8 production in TF-positive tumor cells. Internalization studies in vitro demonstrated that HuMax-TF was efficiently internalized upon binding to TF-positive tumor cells. At the same time, HuMax-TF showed minimal impact on TF procoagulant activity in vitro, as assessed using a chromogenic FXa generation assay and thromboelastography (TEG) analysis.[1] Importantly, HuMax-TF, which showed comparable binding to human and cynomolgus monkey TF, did not induce clear effects on parameters of coagulation at very high doses (up to 100 mg/kg) in cynomolgus monkeys. Tisotumab vedotin induces potent cytotoxicity in TF-positive tumor cells in vitro and was shown to be the most potent of three different TF-specific MMAE-based antibody-drug conjugates in preclinical tumor models in vivo. The dominant mechanism of action of tisotumab vedotin in preclinical models was found to be MMAE-mediated tumor cell killing. Upon binding of TF by TV, the resulting complex is efficiently internalized and trafficked to the lysosome where the linker is enzymatically cleaved, releasing MMAE within the targeted tumor cell.[1,20] Then MMAE binds to tubulin and disrupts microtubule polymerization, resulting in G2/M cell cycle arrest and apoptosis.[1,21] As a cell-permeable molecule, MMAE can also diffuse into the tumor microenvironment where it might induce bystander killing of neighboring dividing cells.[1,20] These antitumor effects are further enhanced by the capacity of TV to bind FcγRIIIa on adjacent

natural killer cells, which was shown to lead efficient to antibody-dependent cellular cytotoxicity of TF-expressing tumor cells.[1,22] Additionally, MMAE-based ADCs have been shown to induce immunogenic cell death, which can activate innate and adaptive immune responses to tumor antigen.[23] In preclinical studies, TV has demonstrated robust antitumor activity in vitro and in xenograft models in vivo, using models derived from multiple solid tumors, including bladder, prostate, lung, pancreas, ovarian, and cervical, which demonstrated differential expression of TF.[1]

These preclinical data led to the conduct of the first-in-human TV clinical trial: innovaTV 201 (NCT02001623), which evaluated the safety, tolerability, pharmacokinetics, and antitumor activity of TV in patients with locally advanced and/or metastatic solid tumors known to express TF are presented.[24] The results of this trial are presented herein; patients with tumor types known to express TF and with susceptibility to microtubule disrupting agents were evaluated.

METHODS

Study Design and Participants

This study was conducted as a phase 1/2, open-label, multicenter, dose-escalation and dose-expansion study. Patients were recruited across 3 sites (Denmark [n=1]; United Kingdom [n=1], United States [n=1]) for the dose-escalation portion and 21 sites (Belgium [n=6]; Denmark [n=2]; Sweden [n=1]; United Kingdom [n=9]; United States [n=3]) for the expansion portion (**Appendix p 2**). Eligible patients had locally advanced and/or metastatic cancer of the bladder, cervix, endometrium, esophagus, non-small cell lung cancer (NSCLC), ovary, prostate (in particular castration-resistant prostate cancer [CRPC]), or squamous cell carcinoma of the head and neck (SCCHN) who had failed or were not eligible to receive the available standard of care.

Eligible patients were aged ≥18 years, had a life expectancy ≥3 months, acceptable organ function, hematologic and coagulation status, Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1·1.[25] Patients with prostate cancer could be included based on bone metastases or prostate specific antigen (PSA). All patients were required to have a tumor biopsy at screening; a fresh biopsy was collected at least 2 weeks before dosing, if no archival tissue was available. There were no requirements for tumor TF expression for eligibility.
Patients were excluded if they had past or current coagulation defects, ongoing major bleeding, long-term antiplatelet or anticoagulant therapy, clinically significant cardiac disease, major surgery within 6 weeks before drug infusion or anticipated during study treatment, open biopsy within 7 days before drug infusion, had another malignancy, or known infection with HIV, hepatitis B virus, or hepatitis C virus. Patients were also excluded if they had received prior therapy with an auristatin derivative, bevacizumab within 12 weeks from first study dose, radiotherapy within 28 days from first study dose, or any other anticancer therapy within five half-lives before first dose.

The study protocol was amended on 22 December 2016 and again on 23 June 2017 after 77 patients were enrolled to implement ocular preventive measures, including the use of lubricating eye drops throughout the study period, steroid eye drops during the first 3 days of each treatment cycle, local ocular vasoconstrictor before treatment infusion, and cooling eye masks worn during treatment infusion, as well as stricter dose adjustment guidance.

The Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each study site approved the protocol, and the study was conducted in accordance with the Declaration of

Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent for participation.

Procedures

The dose-escalation phase of this clinical trial was conducted using a traditional 3 + 3 design. Nonclinical safety studies were conducted in cynomolgus monkeys that were treated with tisotumab vedotin at doses ranging from 1–5 mg/kg. First-in-human dose of 0.3 mg/kg was selected based on 1/10 highest non-severely toxic dose (HNSTD) for TV of 3 mg/kg determined in the pivotal 13 weeks good laboratory practice (GLP)-repeat dose toxicity study (Q3W x 5 doses) in cynomolgus monkeys. Based on adverse events observed in these studies, particularly reversible bone marrow toxicity and low neutrophil counts that showed a nadir between 10 and 18 days after treatment, the Q3W dosing schedule was selected. Patients were enrolled to eight cohorts of TV, ranging from 0·3 to 2·2 mg/kg administered intravenously once every 3 weeks (1Q3W). The decision to proceed to the next dose level in the dose-escalation phase was based on the rate of dose-limiting toxicities (DLT) observed during the first 21-day treatment cycle. If one of the three patients at a given dose developed a DLT, then an additional three patients were added at the same dose level. If none of the three patients, or one of six developed a DLT, then the study continued escalation to the next dose level. The dose level below the dose at which two or more DLTs occurred within six patients was defined as the MTD, and the RP2D.

The dose-expansion phase of the study had a multiple cohort design and enrolled patients in tumor-type cohorts to be treated with TV at the RP2D. Patients were treated for up to four cycles or until disease progression. Recruitment was initiated in five tumor cohorts, including bladder, cervix, endometrium, ovary, and prostate. Following a safety review of data from the ten first

patients recruited and followed for at least one cycle, regardless of indication, recruitment for the lung and esophageal cohort was initiated. Based on preliminary activity data, the cervical and ovarian cohorts were expanded to include a maximum of approximately 55 and 30 patients, respectively. The remaining tumor cohorts recruited approximately 14 patients each. Patients with demonstrated clinical benefit, defined as stable disease or better, had the option to continue treatment for an additional eight cycles or until unacceptable toxicity or disease progression.

Adverse events (AEs) were assessed and reported at each visit according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4·03. Tumor assessments were performed using computed tomography or by magnetic resonance imaging in patients allergic to iodine contrast or at the discretion of the investigator, at screening and every 6 weeks during the study.

Blood samples for PK analysis were collected before and after the infusion at each cycle. Additional samples were collected during cycles 1 and 2 on day 1 (2 hours, 5 hours, and 12 hours after the end of the infusion) and on days 2, 8, and 15. Blood samples were collected throughout the study for analysis of blood coagulation parameters, including prothrombin time (PT) and activated partial thromboplastin time (aPTT) and immunogenicity.

Outcomes

The primary objective of this study was to establish the safety and tolerability of TV, characterized by the incidence of AEs, serious AEs, infusion-related AEs, CTCAE grade ≥3 AEs, and study drug related AEs. A serious AE (SAE) was defined as any AE that required an extended hospitalization, resulted in persistent or significant incapacity/dysfunction, led to a congenital anomaly or birth defect, was deemed medically important, resulted in death, or was fatal or life-threatening. Safety laboratory parameters and safety events of interest, including skin

disorders, bleeding events, and neuropathy were included in the safety analysis. A data-monitoring committee (DMC) evaluated safety data during the study. Causality for DLTs was assessed by the investigators and sponsor in collaboration with the DMC.

Secondary objectives were to establish the maximum-tolerated dose (MTD), to define the recommended phase 2 dose (RP2D), to characterize the pharmacokinetic (PK) profile, and to assess the antitumor activity of TV. PK parameters, including area under the concentration time curve ($AUC_{0\text{-}t}$), maximum concentration (C_{max}), and time to reach maximum concentration (t_{max}), were determined from the concentration-time data, where feasible, for TV and free MMAE by noncompartmental analysis.

Tumor response was investigator assessed per RECIST version 1·1 criteria, with antitumor activity endpoints including objective response (complete response [CR] or partial response [PR]), disease control (CR, PR, or SD), progression-free survival (PFS), and duration of response (DoR). PFS was defined as the number of days from the first day of the first cycle to the first progressive disease (PD) or death. Deaths that occurred within 60 days of the last visit were included in the analysis. DoR was defined as the number of days from the first documented objective tumor response (CR or PR) to the date of first PD or death. Changes in prostate specific antigen (PSA) and cancer antigen (CA) 125 were also monitored where applicable.

Statistical Analyses

The sample size of the dose-escalation phase was calculated as a maximum of 48 patients based on the 3 + 3 design with three to six patients in each dose cohort. The estimated sample size for the dose-expansion phase was 144 patients, which had 76% and 95% power to detect AEs with incidences 1% and 2% respectively. Based on preliminary activity data within the cervical and

ovarian cohorts, the study protocol was amended on 26 September 2017 to allow for the expansion of these cohorts causing the study to exceed the original sample size estimates.

The full analysis population was comprised of patients who were exposed to study drug. This population was used for evaluation of all endpoints. Safety evaluations and PK parameters were summarized descriptively. For the activity analysis, the investigator-assessed objective response rate (ORR) was determined with the corresponding two-sided 95% exact binomial CI. The Kaplan-Meier (KM) method was used to estimate the median months for progression-free survival (PFS) and duration of response (DoR), which were presented with a two-sided 95% CI. Further exploratory analysis of subsets of data may be performed in preparation for subsequent studies. Data analysis was performed using SAS (version 9.4) and R (version 3.5.1). This study is registered with ClinicalTrials.gov, number NCT02001623.[24]

Role of the Funding Source

The funder designed the study in collaboration with a subgroup of investigators, managed the clinical trial database, including oversight of data collection, performed statistical analyses, and provided medical writing assistance. The corresponding author had full access to all the data in the study and had the final responsibility to submit for publication.

RESULTS

This report includes data from the completed dose-escalation phase and the ongoing (data cutoff date of February 1, 2018, except for the cervical cohort activity analysis, which has a cutoff date of July 24, 2017) expansion phase of the innovaTV 201 study. The dose-escalation phase enrolled 27 patients between 9 December 2013 and 18 May 2015, with a mixed population of primary tumor types. Three patients were included in dose cohorts ranging from 0·3 to 2·0

mg/kg, while six patients were included in the 2·2-mg/kg dose cohort. The median age of patients was 62 (interquartile range [IQR] 58–67) years. The median number of prior therapies was 3 (1–14). In the dose-expansion phase, 147 patients were included across seven tumor-type cohorts, including bladder (n=15), cervical (n=34), endometrial (n=14), esophageal (n=15), NSCLC (n=15), ovarian (n=36), and prostate (n=18) between 8 October 2015 and 26 April 2018. The median age of patients was 59 (IQR 52–67) years. The median number of prior therapies across tumor types ranged was 3 (1–9). Patient characteristics are listed in **Table 1**. Patient enrollment and disposition are illustrated in **Figure 1**.

In the dose-escalation phase, all 27 patients received ≥1 dose of TV and were evaluable for DLTs. Three DLTs were identified in the 2·2-mg/kg dose cohort, including type 2 diabetes mellitus, mucositis, and neutropenic fever, all of which were grade 3. Based on these data, the MTD and RP2D were defined as 2·0 mg/kg. There were three deaths reported; none of which were considered related to study drug. Two patients included in the 0·3-mg/kg dose cohort died from disease progression; one patient (SCCHN) included in the 0·6-mg/kg dose cohort died from a pharyngeal tumor hemorrhage. Treatment-emergent AEs for the dose-escalation phase are listed in **Appendix p 3**.

In the dose-expansion phase, 147 patients received ≥1 dose of TV and were evaluated for safety. Of the 147 patients treated, 27 (18%) required 1 or more dose reductions. The median (IQR) follow-up time in these patients was 2·8 (1·4–4·4) months. Across tumor types, the most commonly (occurring in ≥20% of patients) reported treatment-emergent AEs (TEAEs) of any grade were epistaxis (102 [69·4%] of 147 patients), fatigue (82 [55·8%]), nausea (77 [52·4%]), alopecia (64 [43·5%]), conjunctivitis (63 [42·9%]), decreased appetite (53 [36·1%]), constipation (52 [35·4%]), diarrhea (44 [29·9%]), vomiting (42 [28·6%]), neuropathy peripheral (33 [22·4%]),

dry eye (32 [21·8%]), and abdominal pain (30 [20·4%]) (**Table 2**). Treatment-emergent grade ≥3 AEs occurred in 83 (56·5%) of 147 patients. The most commonly (occurring in >2% of patients) reported treatment-emergent grade ≥3 AEs were fatigue (14 (9·5%) of 147 patients), anemia (8 [5·4%]), abdominal pain (6 [4·1%]), hypokalemia (6 [4·1%]), conjunctivitis (5 [3·4%]), hyponatremia (5 [3·4%]), and vomiting (5 [3·4%]). A total of 60 (40·8%) of 147 patients experienced a treatment-emergent grade ≥3 AE deemed related to study drug.

Treatment-emergent SAEs occurred in 67 (45·6%) of 147 patients. The most common treatment-emergent SAEs (occurring in >2% of patients) were vomiting (6 [4·1%]), abdominal pain (5 [3·4%]), and anemia (4 [2·7%]) (**Appendix p 4**). A total of 39 (26·5%) of 147 patients experienced a treatment-emergent SAE deemed related to study drug. Discontinuations related to AEs occurred in 32 (21·8%) of 147 patients, ocular AEs occurred in 11 (7·5%) patients. Six AEs with fatal outcomes occurred in the dose-expansion phase: two patients with general physical health deterioration, one with disease progression, one with metastasis to the central nervous system, one with esophageal metastatic cancer, and one with pneumonia. These events were deemed not related to study drug, with the exception of pneumonia, which was possibly related.

AEs of special interest included bleeding-related events, neuropathy, and ocular events (conjunctivitis, ulceration, keratitis, symblepharon). Epistaxis was the most commonly reported AE, the majority of which were grade 1 in severity (100 of 102). No grade 4–5 bleeding events were reported in the dose-expansion phase. Neuropathy of any grade occurred in 63 (42·9%) of 147 patients with 10 (6·8%) patients experiencing grade ≥3 neuropathy (**Appendix p 5**). The median (SD) time to onset of neuropathy was 8·7 (0·1–26·4) weeks. In patients who experienced neuropathy, 81% (51 of 63) of patients had received prior taxane chemotherapy, the most common of which was paclitaxel. At the time of this analysis, 15·9% (10 of 63) of patients had

neuropathy events resolved, including seven patients with prior taxane. Ocular events of any grade occurred in 88 (59·9%) of 147 patients, with 63 (42·9%) of all patients experiencing conjunctivitis (**Appendix p 6**). Implementation of ocular mitigation strategies substantially reduced the incidence of conjunctivitis, which decreased from 43 (55·8%) of 77 patients to 20 (28·6%) of 70 patients (**Appendix p 6**).

The PK profile of TV was assessed in the dose-escalation phase. The profiles of mean blood concentration for TV and free MMAE are presented in the **Appendix p 9**. Increases in exposure to TV and free MMAE were proportional to dose. The C_{max} of TV occurred shortly after the end of infusion, whereas levels of free MMAE peaked 1 week following infusion. Only low levels of free MMAE were detected in the systemic circulation. Parameters reflecting exposure, including C_{max} and $AUC_{0\text{-}t}$, increased proportionally over the dose ranges examined (**Appendix p 7**). When TV was dosed at 2·0 mg/kg (n=3), the mean C_{max} value was 32·3 µg/mL and the mean $AUC_{0\text{-}t}$ value was 1256·4 h·µg/mL. Following a single-dose administration of TV at 2·0 mg/kg, the mean time-to-peak plasma concentration (t_{max}) was observed 1·2 hours from the start of the infusion. The mean (SD) half-life for TV at 2·0 mg/kg was estimated to be 1·71 (0·20) days.

Blood coagulation parameters, including PT and aPTT, were not altered by treatment with TV (**Appendix p 10**). Across dose-escalation cohorts, the mean (SD) PT value at baseline was 11·5 (1·3) seconds (n=18) compared with 11·7 (1·5) seconds (n=17) at study completion, while the mean (SD) aPTT value at baseline was 28.2 (3·3) seconds (n=25) compared with 27·1 (3·2) seconds (n=23) at study completion.

In the dose-escalation phase, of the 27 patients evaluated, one patient with metastatic cervical cancer achieved a partial response at the 1.2 mg/kg dose level (antitumor activity reported in **Appendix p 8**). This patient had received three prior treatment lines before study entry. In the

dose-expansion phase, 147 patients were evaluable for investigator-assessed response. Across tumor types, the confirmed ORR for the full analysis set was 15·6% (95% CI: 10·2%–22·5%; 23 of 147 patients). All responses were partial. For each tumor type, the confirmed ORR was 26·7% (4/15) in bladder, 26·5% (9/34) in cervical, 13·9% (5/36) in ovarian, 13·3% (2/15) in esophageal, 13·3% (2/15) in NSCLC, 7·1% (1/14) in endometrium, and 0/18 in prostate (**Table 3**). Maximum percentage change from baseline in tumor size for each dose-expansion cohort is shown in **Figure 2**. Across tumor types, the median confirmed DoR was 5·7 (3·0–9·5) months (swimmer plots for individual responders [**Figure 3**]) and the median PFS was 3·0 (2·8–4·1) months with 89 events.

DISCUSSION

This multicenter, first-in-human clinical trial has validated the targeting of TF for the treatment of advanced cancer, and has shown that TV has an encouraging antitumor activity in heavily pretreated patients with multiple different tumors known to express TF. The safety profile of TV 2·0 mg/kg 1Q3W was generally consistent with other MMAE-based ADCs, although epistaxis and conjunctivitis were reported at increased incidences with TV. Bleeding events other than epistaxis were consistent with those expected for a population of patients treated with chemotherapy indicating that epistaxis was not a signal for a general bleeding disorder. Ocular toxicities have been reported with ADCs that include ravtansine (DM4) and monomethyl auristatin F (MMAF); however, they are rarely described for ADCs that utilize MMAE.[26] As a result, it is speculated that the increased incidences of epistaxis and conjunctivitis are related to underlying inflammation or increased localized TF expression in the affected area. An ocular mitigation plan was implemented during the study that reduced the frequency and severity of ocular AEs, including conjunctivitis. Similar ocular mitigation strategies have been used

prophylactically with other ADCs to manage ocular events. Peripheral neuropathy, a known toxicity of MMAE-based ADCs, was observed in patients treated with TV; most events reported were mild to moderate in severity and occurred in patients with prior exposure to taxanes. Three DLTs were reported in the 2·2-mg/kg dose cohort of the dose-escalation phase, one of which was type 2 diabetes mellitus. Hyperglycemia has been previously described as a DLT in other MMAE-based ADCs, such as brentuximab vedotin and DMOT4039A, and is likely to be due to the cytotoxic payload.[27,28]

This trial validates the use of an ADC-based approach to target TF, the main initiator of the extrinsic pathway of blood coagulation.[4] Coagulation parameters, such as PT and aPTT, were not affected by TV administration. Furthermore, despite the incidence of grade 1–2 epistaxis in 69·4% of patients receiving TV, no grade 4–5 bleeding events were observed in patients in the dose-expansion phase. These findings corroborate previous nonclinical toxicology studies of TV in cynomolgus monkeys, which demonstrated no significant impact on functional bleeding time or systemic parameters of coagulation at doses up to 5 to 6 mg/kg.[1]

Although not designed or powered to assess antitumor activity, this trial reports encouraging antitumor activity for TV in a broad population of patients with heavily pretreated, locally advanced and/or metastatic cancers of the bladder, cervix endometrium, esophagus, lung, and ovary. Biopsy or archived samples were collected at study entry for all patients, and a currently ongoing analysis will assess the correlation of tumor TF expression and the antitumor activity of TV to assess the value of TF expression as a biomarker for treatment response.

These data support the further investigation of TV. Multiple studies are underway, including innovaTV 207 and innovaTV 204. InnovaTV 207 (NCT03485209) is an ongoing phase 2 study evaluating the activity, safety, and tolerability of TV monotherapy administered every 3 weeks in

patients with relapsed, locally advanced or metastatic colorectal cancer, squamous NSCLC, pancreatic cancer, or SCCHN.[29] Based on encouraging preliminary activity seen in the cervical cancer cohort, innovaTV 204 (NCT03438396) is an ongoing phase 2 study evaluating the activity, safety, and tolerability of TV monotherapy in patients with previously treated, recurrent or metastatic cervical cancer that had progressed during or after treatment with standard first-line therapy.[30]

CONTRIBUTORS

JSDB, UL, RAR, SG, and KW conceived, designed, and planned the study. JSDB, UL, NC, DSH, FCT, JPM, HTA, RP, RHJ, DN, BMS, JFS, JY, JEA, PMMS, MDF, DC and ED acquired the data. KW analyzed the data and all authors helped interpret the data. All authors were involved in development, reviewed or revised the manuscript for intellectual content, and gave approval for submission of the manuscript. JSDB and UL were responsible for the final decision to submit for publication.

DECLARATION OF INTERESTS

Dr De Bono reports personal fees from AstraZeneca, personal fees from Astellas, personal fees from Genentech, personal fees from Roche, personal fees from GSK, personal fees from Merck, personal fees from Genmab, personal fees from Sanofi-Aventis, personal fees from Pfizer, outside the submitted work. Dr Hong reports grants from Bayer, grants from Lilly, grants from Genentech, grants from LOXO, grants from Pfizer, grants from Amgen, grants from Mirati, grants from Ignyta, grants from Merck, grants from Daichii-Sanko, grants from Eisai; personal fees from Mirna, personal fees from LOXO, consulting/advisor role for Bayer, consulting/advisor role for Baxter, consulting/advisor role for Guidepoint global, ownership interest in Oncoresponse, grants from Adaptimmune, grants from Abbvie, grants from Astra-

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DATA SHARING

The de-identified data that support the findings of this study are available on request to bona fide researchers who provide a methodologically sound proposal. The data will be made available 24 months following study completion. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

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FIGURE LEGENDS

Figure 1. Patient enrollment and disposition in innovaTV 201 (dose escalation and expansion).

Figure 2. Maximum reduction in tumor size in the various expansion study cohorts recruiting patients with bladder, cervix, endometrium, esophagus, NSCLC, ovary, and prostate cancers.

The black bars indicate tumor size at first scan, and the gray bars indicate best response.

*Target lesions were lymph nodes only and the sum of the target lesions post-baseline was <10 mm. The percentage change from baseline was set to -100. †Disease progression due to new lesion. ‡Percent change from baseline is 287·5%.

Figure 3. Duration of response in individual responders.

Table 1. Patient Characteristics

Characteristic	Dose Escalation	Dose Expansion
Total patients, No.	27	147
Age, median (IQR), y	63 (58–67)	59 (52–67)
Female, No. (%)	18 (66·7)	101 (68·7)
Male, No. (%)	9 (33·3)	46 (31·3)
Race		
White	27 (100)	136 (92·5)
Black	0	2 (1·4)
Asian	0	4 (2·7)
Other	0	3 (2·0)
Missing	0	2 (1·4)
ECOG PS, No. (%)		
0	13 (48·1)	60 (40·8)
1	13 (48·1)	86 (58·5)
Missing	1 (3·8)	1 (0·7)
Primary tumor type, No. (%)		
Bladder	2 (7·4)	15 (10·2)
Cervix	2 (7·4)	34 (23·1)
Endometrium	3 (11·1)	14 (9·5)
Esophagus	4 (14·8)	15 (10·2)
NSCLC	4 (14·8)	15 (10·2)
Ovary	7 (25·9)	36 (24·5)
Prostate	4 (14·8)	18 (12·3)
SCCHN	1 (3·8)	–
Number of prior therapies, median (range)		
All	3 (1–14)	3 (1–9)
Bladder	–	2 (1–5)
Cervix	–	2 (1–5)
Endometrium	–	1.5 (1–5)
Esophagus	–	2 (1–4)
NSCLC	–	2 (1–5)
Ovary	–	4 (2–9)
Prostate	–	4 (3–7)
SCCHN	–	–

Abbreviations: ECOG=Eastern Cooperative Oncology Group; PS=performance status; SCCHN= squamous cell carcinoma of the head and neck.

Table 2. Treatment-Emergent AEs (Occurring in >10% of Patients or with Grade ≥ 3) in the Dose-Expansion Phase

	n=147			
Preferred term	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Any AE, No. (%)	65 (44)	78 (53·1)	9 (6·1)	6 (4·1)
Epistaxis	102 (69·4)	0	0	0
Nausea	74 (50·3)	3 (2·0)	0	0
Fatigue	68 (46·3)	14 (9·5)	0	0
Alopecia	64 (43·5)	0	0	0
Conjunctivitis	58 (39·5)	5 (3·4)	0	0
Decreased appetite	51 (34·7)	2 (1·4)	0	0
Constipation	50 (34·0)	2 (1·4)	0	0
Diarrhea	42 (28·6)	2 (1·4)	0	0
Vomiting	37 (25·2)	5 (3·4)	0	0
Dry eye	32 (21·8)	0	0	0
Neuropathy peripheral	31 (21·1)	2 (1·4)	0	0
Weight decreased	25 (17·0)	0	0	0
Abdominal pain	24 (16·3)	6 (4·1)	0	0
Pruritus	22 (15·0)	0	0	0
Myalgia	22 (15·0)	0	0	0
Arthralgia	21 (14·3)	0	0	0
Dyspnea	21 (14·3)	2 (1·4)	0	0
Rash	21 (14·3)	1 (0·7)	0	0
Insomnia	20 (13·6)	1 (0·7)	0	0
Back pain	18 (12·2)	1 (0·7)	0	0
Cough	18 (12·2)	0	0	0
Headache	17 (11·6)	0	0	0
Hypokalemia	16 (10·9)	6 (4·1)	0	0
AST increased	16 (10·9)	1 (0·7)	0	0
Peripheral sensory neuropathy	13 (8·8)	3 (2·0)	0	0
Pyrexia	13 (8·8)	1 (0·7)	0	0
ALT increased	13 (8·8)	2 (1·4)	0	0
Uncoded	13 (8·8)	1 (0·7)	0	0
Hypomagnesemia	12 (8·2)	2 (1·4)	0	0
Anemia	12 (8·2)	8 (5·4)	0	0
Muscular weakness	11 (7·5)	1 (0·7)	0	0
Urinary tract infection	10 (6·8)	2 (1·4)	0	0
Mucosal inflammation	10 (6·8)	1 (0·7)	0	0
Stomatitis	10 (6·8)	1 (0·7)	0	0
Upper respiratory tract infection	8 (5·4)	1 (0·7)	0	0
Vaginal hemorrhage	7 (4·8)	2 (1·4)	0	0
Blood ALP increased	7 (4·8)	1 (0·7)	0	0
Neutropenia	6 (4·1)	3 (2·0)	0	0
Ulcerative keratitis	6 (4·1)	0	1 (0·7)	0
Anxiety	5 (3·4)	1 (0·7)	0	0
Asthenia	5 (3·4)	1 (0·7)	0	0
Malaise	5 (3·4)	1 (0·7)	0	0
Dehydration	4 (2·7)	2 (1·4)	0	0
Hypertension	4 (2·7)	2 (1·4)	0	0
Blood CPK increased	4 (2·7)	1 (0·7)	0	0
Peripheral motor neuropathy	4 (2·7)	1 (0·7)	0	0
Hyponatremia	3 (2·0)	3 (2·0)	2 (1·4)	0
Colitis	3 (2·0)	2 (1·4)	0	0
GGT increased	3 (2·0)	2 (1·4)	0	0
Lower respiratory tract infection	3 (2·0)	2 (1·4)	0	0
Dysphagia	2 (1·4)	2 (1·4)	0	0
Gastroenteritis	2 (1·4)	1 (0·7)	0	0
Infection	2 (1·4)	1 (0·7)	0	0
Polyneuropathy	2 (1·4)	2 (1·4)	0	0
Tumor pain	2 (1·4)	1 (0.7)	0	0
Hyperglycemia	1 (0·7)	2 (1·4)	0	0
Hypoacusis	1 (0·7)	1 (0·7)	0	0
Hypophosphatemia	1 (0·7)	2 (1·4)	0	0
Lymphocyte count decrease	1 (0·7)	2 (1·4)	0	0

Neutrophil count decrease	1 (0·7)	1 (0·7)	0	0
Pulmonary embolism	1 (0·7)	1 (0·7)	0	0
Hydronephrosis	0	2 (1·4)	0	0
Ankle fracture	0	1 (0·7)	0	0
Cellulitis	0	1 (0·7)	0	0
Clostridium difficile colitis	0	1 (0·7)	0	0
Corneal lesion	0	1 (0·7)	0	0
Demyelinating polyneuropathy	0	1 (0·7)	0	0
Device failure	0	1 (0·7)	0	0
General physical health deterioration	0	1 (0·7)	0	2 (1·4)
GI hemorrhage	0	1 (0·7)	0	0
GI ulcer hemorrhage	0	1 (0·7)	0	0
Hemorrhage	0	1 (0·7)	0	0
Hypoxia	0	1 (0·7)	0	0
Ischemic stroke	0	1 (0·7)	0	0
Kidney infection	0	1 (0·7)	0	0
Medical device site hemorrhage	0	1 (0·7)	0	0
Metastases to central nervous system	0	1 (0·7)	0	1 (0·7)
Pneumonia	0	1 (0·7)	0	1 (0·7)
Postoperative wound infection	0	1 (0·7)	0	0
Pyelonephritis	0	1 (0·7)	0	0
Respiratory tract infection	0	1 (0·7)	0	0
Sepsis	0	1 (0·7)	1 (0·7)	0
Small intestine obstruction	0	1 (0·7)	0	0
Stress fracture	0	1 (0·7)	0	0
Subileus	0	1 (0·7)	0	0
Tumor hemorrhage	0	1 (0·7)	0	0
Urethral stenosis	0	1 (0·7)	0	0
Urethritis	0	1 (0·7)	0	0
Urosepsis	0	1 (0·7)	0	0
Febrile neutropenia	0	0	2 (1·4)	0
Diabetes mellitus inadequate control	0	0	1 (0·7)	0
Hyperbilirubinemia	0	0	1 (0·7)	0
Hypoglycemia	0	0	1 (0·7)	0
Neutropenic sepsis	0	0	1 (0·7)	0
Esophageal perforation	0	0	1 (0·7)	0
Disease progression	0	0	0	1 (0·7)
Esophageal cancer metastatic	0	0	0	1 (0·7)

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; GGT=gamma-glutaminetransferase; TEAE=treatment-emergent adverse event.

Table 3. Antitumor Activity in the Dose-Expansion Phase

Response*	All (n=147)	Bladder (n=15)	Cervix (n=34)	Endometrium (n=14)	Esophagus (n=15)	NSCLC (n=15)	Ovary (n=36)	Prostate (n=18)
ORR, No. (%) (95% CI) – Full analysis set†	23 (15·6) (10·2–22·5)	4 (26·7) (7·8–55·1)	9 (26·5) (12·9–44·4)	1 (7·1) (0·2–33·9)	2 (13·3) (1·7–40·5)	2 (13·3) (1·7–40·5)	5 (13·9) (4·7–29·5)	0‡ (0–0·2)

*Confirmed responses per RECIST, per investigator review. Six patients in the prostate cohort did not have measurable disease at baseline, therefore responses were evaluated by PSA levels. †The full analysis set was comprised of patients who were exposed to study drug. ‡Neither radiographic imaging or PSA levels indicated a response in these patients.
Abbreviation: ORR=overall response rate.

Figure 1. Patient enrollment and disposition in innovaTV 201 (dose escalation and expansion).

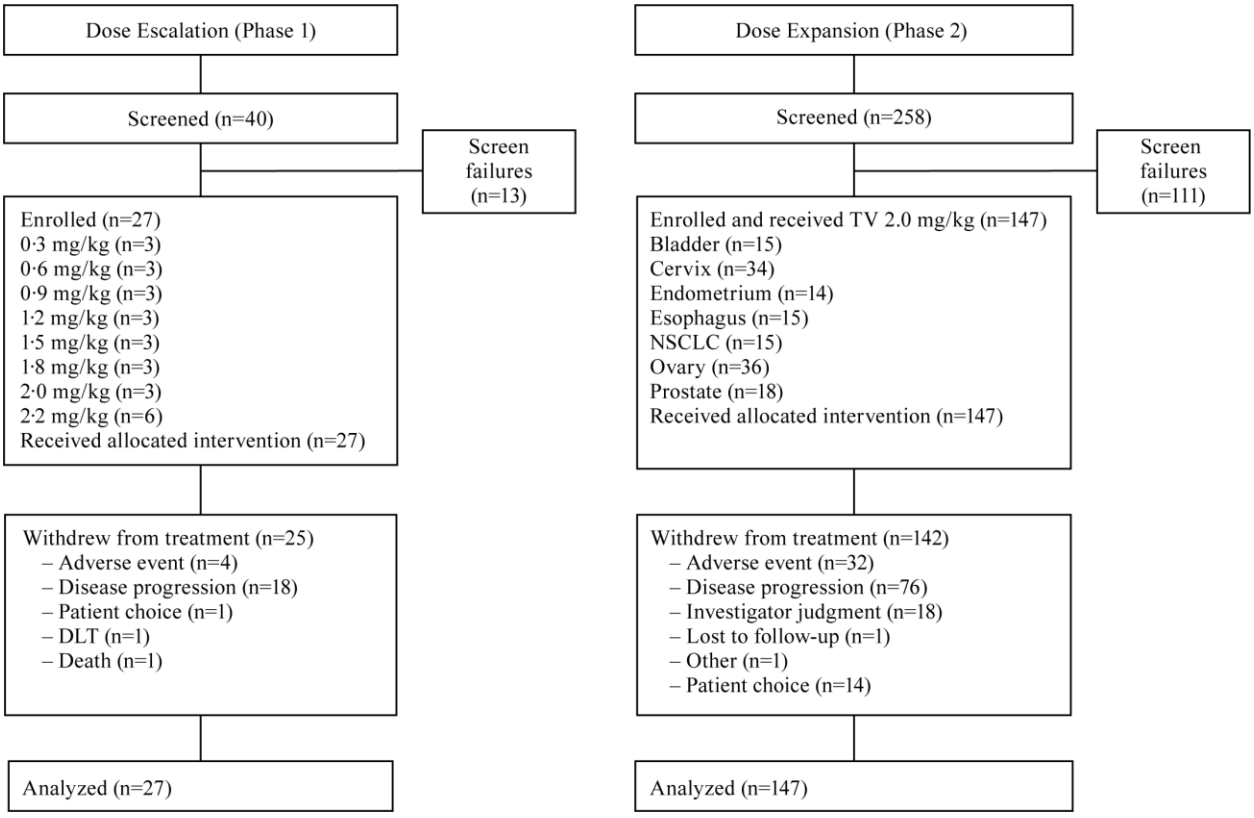


Figure 2. Maximum percentage reduction in tumor size in the various expansion study cohorts recruiting patients with bladder, cervix, endometrium, esophagus, NSCLC, ovary, and prostate cancers.

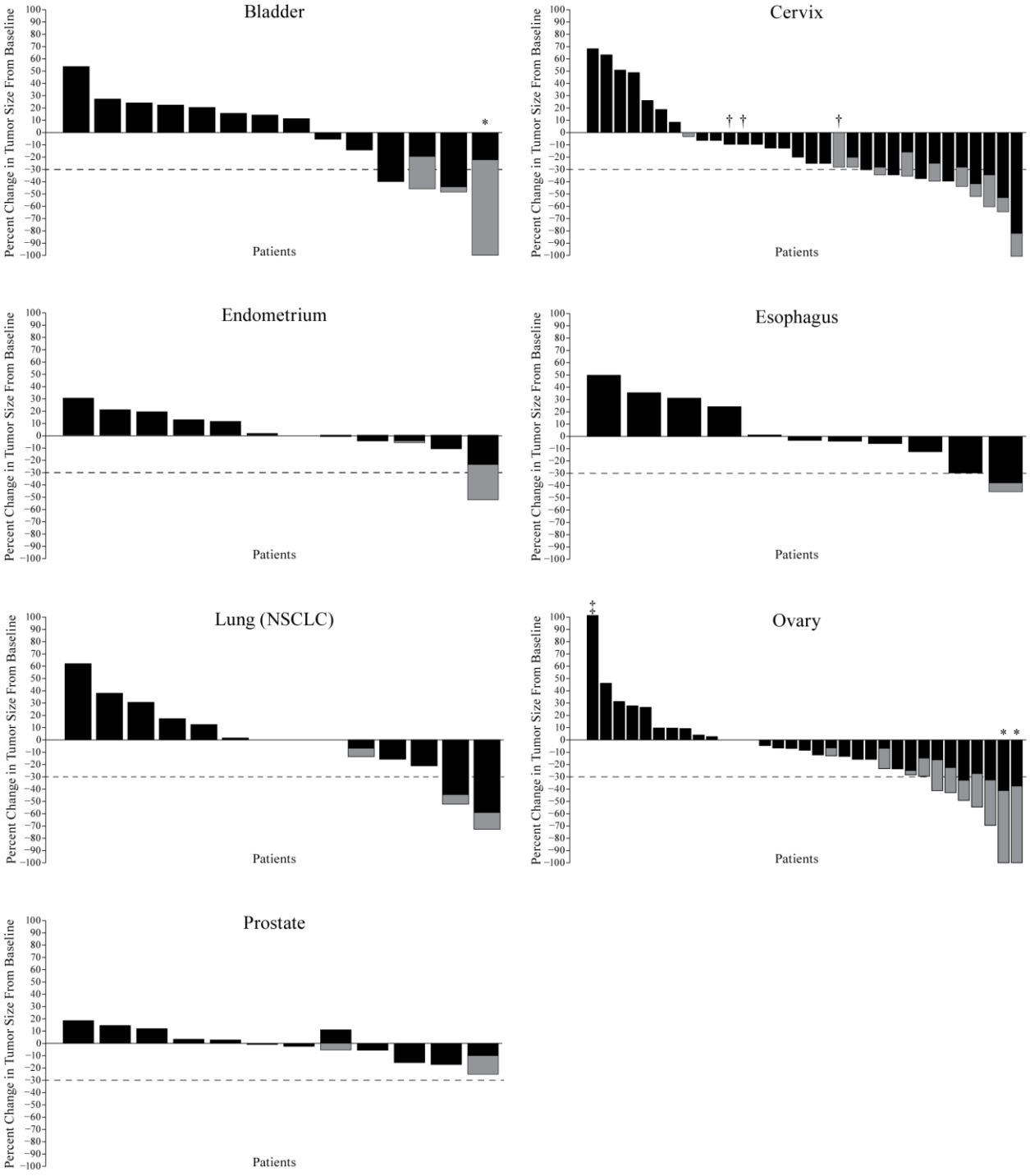
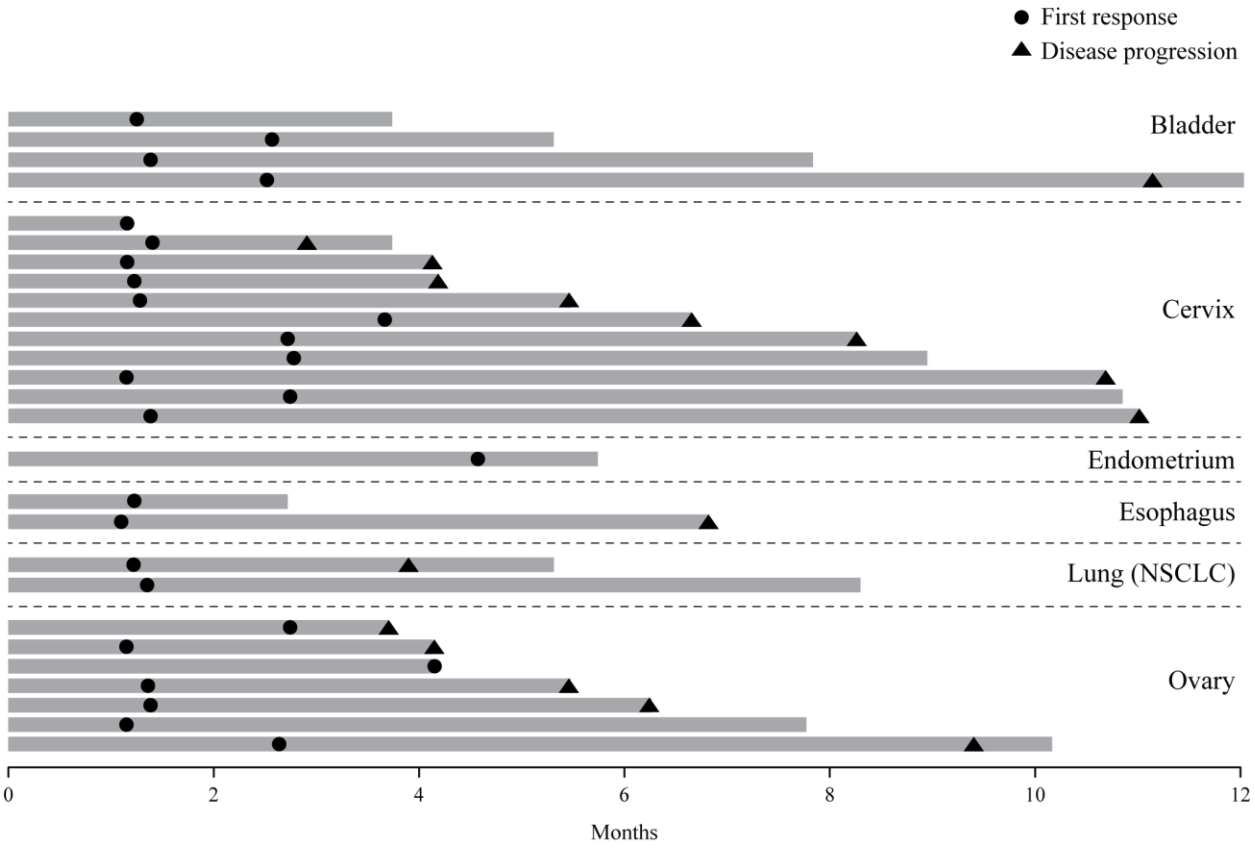


Figure 3. Duration of response in individual responders.



First-in-human study of tisotumab vedotin in advanced and/or metastatic solid tumours: a multicentre, phase 1/2 trial

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Supplementary Information

Patient Recruitment

Patients were recruited across 3 sites (Denmark [n=1]; United Kingdom [n=1], United States [n=1]) for the dose-escalation portion and 21 sites (Belgium [n=6]; Denmark [n=2]; Sweden [n=1]; United Kingdom [n=9]; United States [n=3]) for the expansion portion.

Site Name	Principal Investigator	Number of Patients Enrolled
Dose-escalation Phase		
Royal Marsden Hospital	Johann de Bono	11
Rigshospitalet	Ulrik Lassen	9
The University of Texas MD Anderson Cancer Center	David S Hong	7
Dose-expansion Phase		
Universitair Ziekenhuis Leuven Multidisciplinair Borstcenturm	Nicole Concin	17
The Christie NHS Foundation- Clinical Trial Pharmacy	Emma Dean	13
The University of Texas MD Anderson Cancer Center	David S Hong	12
Rigshospitalet	Ulrik Lassen	11
Newcastle Hospitals NHS Foundation Trust	Ruth Plummer	10
Sarah Cannon Research Institute London	Hendrik-Tobias Arkenau	10
Royal Marsden Hospital	Johann de Bono	9
Clinique Universitaires Saint-Luc	Jean-Pascal Machiels	9
Valindre NHS Trust	Robert Hugh Jones	9
Herlev and Gentofte Hospital	Dorte Nielsen	7
University College London Hospitals	Martin David Forster	7
University of Miami	Brian Slomovitz	6
Sarah Cannon Research Institute-Cincinnati	Melissa Johnson	6
Karolinska University Hospital Solna	Jeffrey Yachin	5
Guy's and Saint Thomas' NHS Foundation Trust	James F Spicer	5
Beatson Cancer Centre Glasgow	Robert Hugh Jones	4
Centre Hospitalier Universitaire de Liège	Christine Gennigens	2
The Leeds Teaching Hospitals NHS Trust	Chris Twelves	2
Centre Hospitalier Universitaire Ambroise Paré	Stephane Holbrechts	1
Grand Hôpital de Charlerai- Notre Dame	Jean-Luc Canon	1
CHU UCL NAMAR- Sainte Elisabeth	Jean-Charles Goeminne	1

Table S1. Treatment-Emergent AEs (Occurring in >10% of Patients or with Grade ≥ 3) in the Dose-Escalation Phase

	All Doses (n=27)			
Preferred term	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Any AE, No. (%)	8 (30)	16 (59)	0	3 (11)
Epistaxis	13 (48)	0	0	0
Fatigue	9 (33)	4 (15)	0	0
Pyrexia	8 (30)	0	0	0
Constipation	8 (30)	0	0	0
Alopecia	8 (30)	0	0	0
Nausea	8 (30)	0	0	0
Decreased appetite	7 (26)	0	0	0
Anemia	7 (26)	4 (15)	0	0
Diarrhea	5 (19)	1 (4)	0	0
Arthralgia	5 (19)	0	0	0
Mucosal inflammation	4 (15)	1 (4)	0	0
Pruritus	4 (15)	0	0	0
Rash (maculopapular)	4 (15)	0	0	0
Nasal congestion	4 (15)	0	0	0
Hypokalemia	4 (15)	1 (4)	0	0
Vomiting	4 (15)	0	0	0
ALT increased	4 (15)	0	0	0
Vision blurred	4 (15)	0	0	0
Headache	4 (15)	0	0	0
Hematuria	4 (15)	0	0	0
Tachycardia	4 (15)	0	0	0
Urinary tract infection	4 (15)	0	0	0
Abdominal pain	3 (11)	3 (11)	0	0
Conjunctivitis	3 (11)	0	0	0
Conjunctival hemorrhage	3 (11)	0	0	0
Neuropathy peripheral	3 (11)	0	0	0
Rash	3 (11)	0	0	0
Weight decrease	3 (11)	0	0	0
Back pain	3 (11)	0	0	0
Dyspnea	2 (7)	1 (4)	0	0
Transaminase increased	2 (7)	1 (4)	0	0
Pain in extremity	2 (7)	1 (4)	0	0
Lymphocyte count decreased	1 (4)	1 (4)	0	0
Ascites	1 (4)	2 (7)	0	0
Hyponatremia	0	3 (11)	0	0
Intestinal obstruction	0	2 (7)	0	0
Gastritis	0	1 (4)	0	0
Small intestine obstruction	0	1 (4)	0	0
Cystitis *escherichia*	0	1 (4)	0	0
Diabetes mellitus	0	1 (4)	0	0
Klebsiella infection	0	1 (4)	0	0
Febrile neutropenia	0	1 (4)	0	0
Guillain-barre syndrome	0	1 (4)	0	0
Acute kidney injury	0	1 (4)	0	0
Platelet count decreased	0	1 (4)	0	0
Disease progression	0	0	0	2 (7)
Pharyngeal hemorrhage	0	0	0	1 (4)

Abbreviation: AE=adverse event.

Table S2. Treatment-Emergent Serious Adverse Events (Occurring in >1% of Patients) in the Dose-Expansion Phase

Preferred term	n=147
Any serious adverse event, No. (%)	67 (45·6)
Vomiting	6 (4·1)
Abdominal pain	5 (3·4)
Anemia	4 (2·7)
Hematuria	3 (2·0)
Constipation	3 (2·0)
Diarrhea	3 (2·0)
General physical health deterioration	3 (2·0)
Hyponatremia	3 (2·0)
Infection	3 (2·0)
Malaise	2 (1·4)
Vaginal hemorrhage	2 (1·4)
Colitis	2 (1·4)
Conjunctivitis	2 (1·4)
Dysphagia	2 (1·4)
Febrile neutropenia	2 (1·4)
Hypokalemia	2 (1·4)
Lower respiratory tract infection	2 (1·4)
Metastases to central nervous system	2 (1·4)
Nausea	2 (1·4)
Pneumonia	2 (1·4)
Sepsis	2 (1·4)
Urinary tract infection	2 (1·4)

Table S3. Incidence of Neuropathy Adverse Events in the Dose-Expansion Phase

	n=147	
Preferred term	**All Grade**	**Grade ≥3**
Any neuropathy event, No. (%)	63 (42·9)	10 (6·8)
Neuropathy peripheral	33 (22·4)	2 (1·4)
Peripheral sensory neuropathy	16 (10·9)	3 (2·0)
Muscular weakness	12 (8·2)	1 (0·7)
Peripheral motor neuropathy	5 (3.4)	1 (0·7)
Paresthesia	4 (2·7)	0
Polyneuropathy	4 (2·7)	2 (1·4)
Dysesthesia	3 (2·0)	0
Gait disturbance	2 (1·4)	0
Hypoesthesia	2 (1·4)	0
Demyelinating polyneuropathy	1 (0·7)	1 (0·7)
Guillain-Barré syndrome	1 (0·7)	0
Muscular atrophy	1 (0·7)	0

Table S4. Incidence of Ocular Adverse Events in the Dose-Expansion Phase

Preferred term	All Patients (n=147)		Before mitigation (n=77)		After mitigation (n=70)	
	All Grade	Grade ≥3	Patients	AEs, No.	Patients	AEs, No.
Any ocular event, No. (%)*	88 (59·9)	5 (3·4)	50 (64·9)	85	38 (54·3)	79
Conjunctivitis	63 (42·9)	5 (3·4)	43 (55·8)	59	20 (28·6)	31
Dry eye	32 (21·8)	0	13 (16·9)	15	19 (27·1)	20
Conjunctival ulcer	6 (4·1)	0	1 (1·3)	1	5 (7·1)	5
Conjunctival hyperemia	4 (2·7)	0	0	0	4 (5·7)	5
Conjunctival scar	4 (2·7)	0	1 (1·3)	1	3 (4·3)	3
Keratitis	4 (2·7)	0	1 (1·3)	2	3 (4·3)	3
Noninfective conjunctivitis	4 (2·7)	0	1 (1·3)	1	3 (4·3)	3
Conjunctival hemorrhage	3 (2·0)	0	3 (3·9)	5	0	0
Symblepharon	3 (2·0)	0	0	0	3 (4·3)	3
Conjunctival disorder	2 (1·4)	0	0	0	2 (2·9)	3
Seasonal allergy	2 (1·4)	0	1 (1.3)	1	1 (1·4)	1
Conjunctival staining	1 (0·7)	0	0	0	1 (1·4)	1
Conjunctivitis allergic	1 (0·7)	0	0	0	1 (1·4)	1

*Most patients with conjunctivitis experienced other ocular events.
Abbreviation: AE=adverse event.

Table S5. Pharmacokinetic Parameters of Tisotumab Vedotin by Dose Cohort After a Single Dose

Dose level (mg/kg)	Patients, No.	AUC_{0-t}		C_{max}		t_{max}	
		Mean (h·µg/mL)	CV (%)	Mean (µg/mL)	CV (%)	Mean (h)	CV (%)
0·3	3	59·2	3·1	4·8	12·4	1·5	72·7
0·6	3	368·4	8·2	12·2	9·5	1·2	13·0
0·9	3	601·9	16·9	19·8	17·3	1·3	11·8
1·2	3	1084·7	9·3	34·7	18·5	1·2	11·7
1·5	3	795·0	19·0	23·1	21·1	1·1	9·6
1·8	3	1504·8	49·5	35·4	39·2	1·2	14·3
2·0	3	1256·4	33·1	32·3	22·1	1·2	7·5
2·2	6	2037·1	33·7	55·5	10·3	1·1	12·5

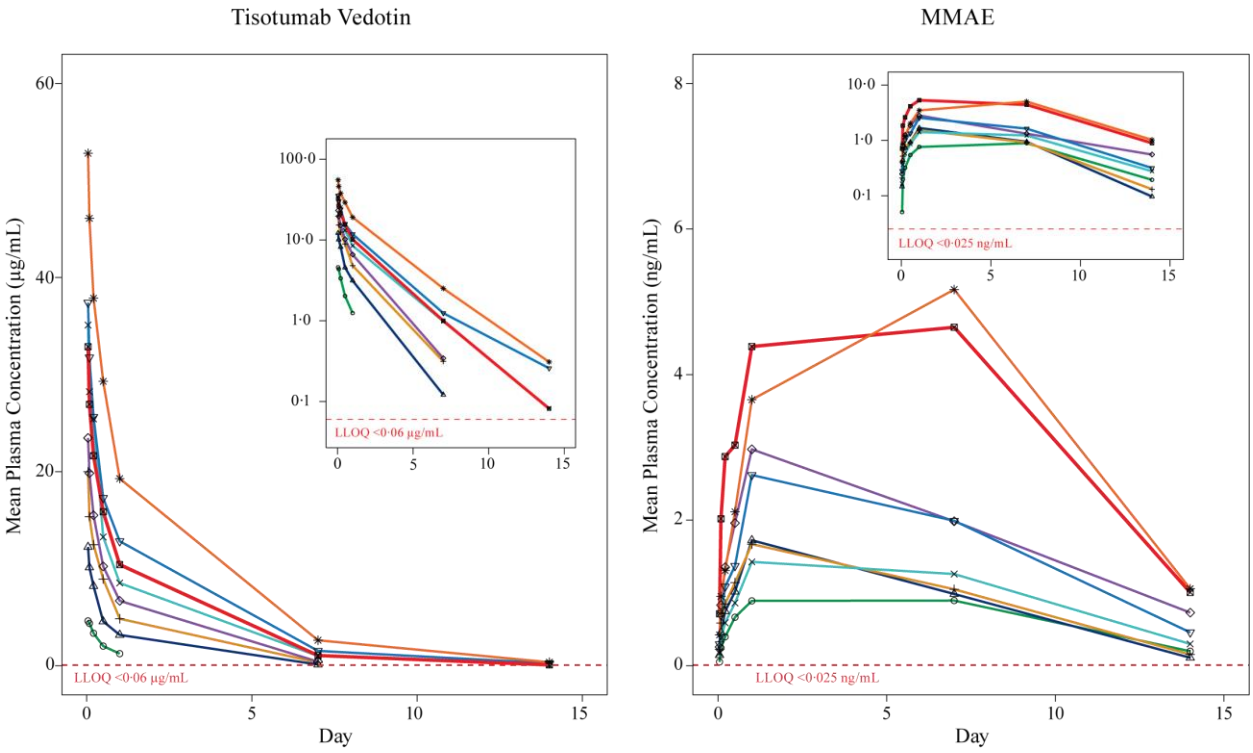
Abbreviations: AUC_{0-t} = area under the concentration time curve; C_{max}=maximum concentration; CV=coefficient of variation; t_{max}=time to reach maximum concentration.

Table S6. Antitumor Activity by Dose Cohort in the Dose-Escalation Phase

Response Evaluation*	All Doses (n=27)	0·3 mg/kg (n=3)	0·6 mg/kg (n=3)	0·9 mg/kg (n=3)	1·2 mg/kg (n=3)	1·5 mg/kg (n=3)	1·8 mg/kg (n=3)	2·0 mg/kg (n=3)	2·2 mg/kg (n=6)
PR, No. (%)	1 (3·7)	0	0	0	1 (33·3)	0	0	0	0
SD, No. (%)	11 (40·7)	0	1 (33·3)	1 (33·3)	1 (33·3)	0	3 (100)	1 (33·3)	4 (66·7)
PD, No. (%)	14 (51·9)	3 (100.0)	1 (33·3)	2 (66·7)	1 (33·3)	3 (100)	0	2 (66·7)	2 (33·3)
NE,[†] No. (%)	1 (3·7)	0	1 (33·3)	0	0	0	0	0	0

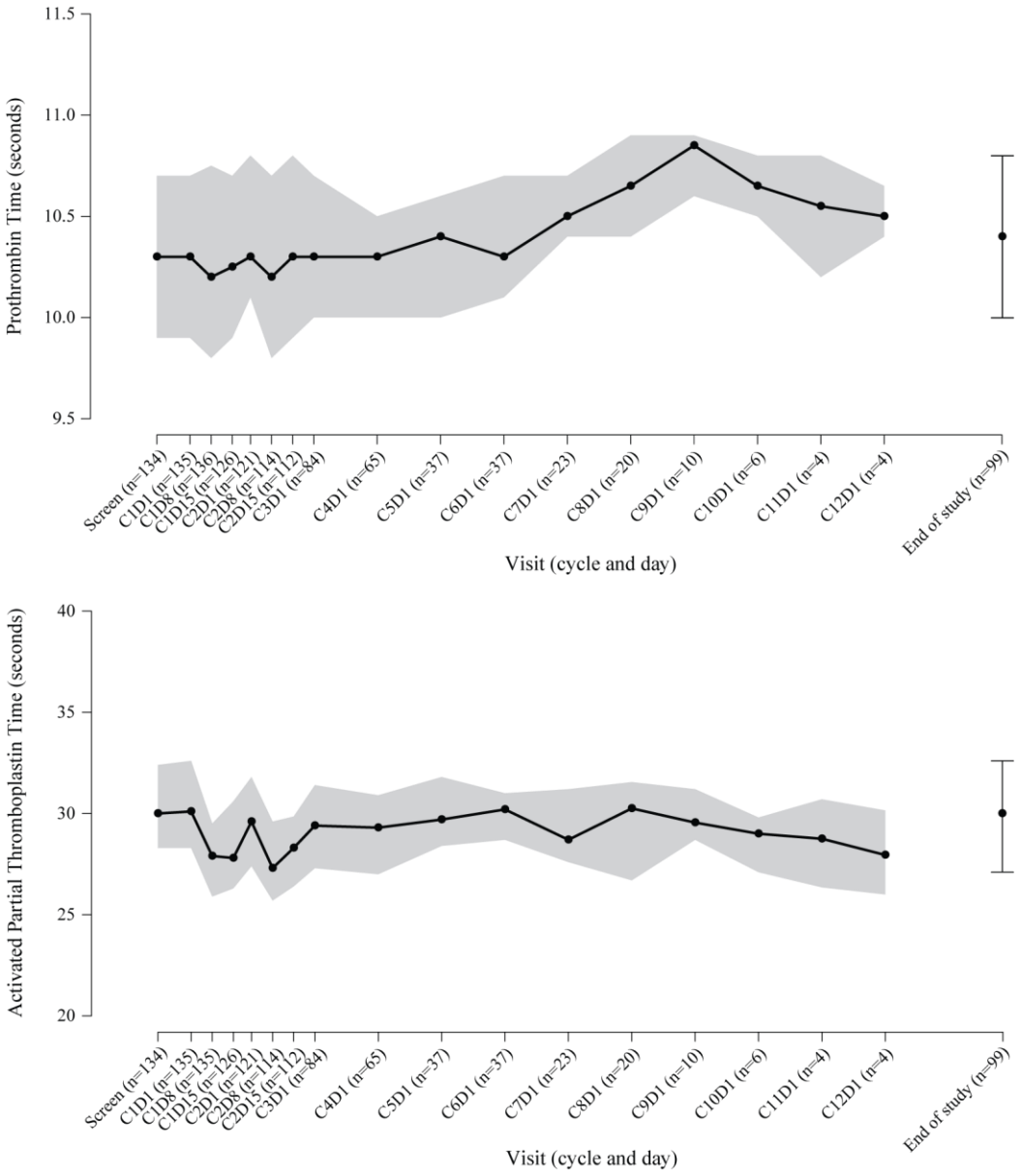
*Confirmed responses per RECIST, per investigator review. [†]Patient died prior to first scan.
NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

Figure S1. Mean plasma concentration-time profiles for tisotumab vedotin and free MMAE at cycle 1 by dose-escalation cohort.



Three patients were included in dose cohorts ranging from 0·3 to 2·0 mg/kg, while six patients were included in the 2·2-mg/kg dose cohort.
Abbreviations: LLOQ=lower limit of quantitation; MMAE=monomethyl auristatin E.

Figure S2. Prothrombin time (PT) and activated partial thromboplastin time in dose-expansion phase.



Black line indicates the median value. The shaded region and error bars indicate the IQR.

Full Study Protocol

The remainder of the web appendix is dedicated to the approved study protocol.